

meet their professed standards of identity, strength, quality, and purity.

(iv) An application pursuant to section 505(b) of the act is approved for the drug.

(v) The preparation contains 0.25 percent of tyloxapol and 0.02 percent of benzalkonium chloride.

(vi) The label bears a conspicuous warning to keep the drug out of the reach of children and the labeling bears, in juxtaposition with the dosage recommendations, a clear warning that if irritation occurs, persists, or increases, use of the drug should be discontinued and a physician consulted. The labeling includes a statement that the dropper or other dispensing tip should not touch any surface, since this may contaminate the solution.

(29) [Reserved]

(b) [Reserved]

[39 FR 11680, Mar. 29, 1974, as amended at 42 FR 36994, July 19, 1977; 52 FR 15892, Apr. 30, 1987; 52 FR 30055, Aug. 12, 1987; 55 FR 31779, Aug. 3, 1990; 57 FR 58374, Dec. 9, 1992; 58 FR 49898, Sept. 23, 1993; 59 FR 4218, Jan. 28, 1994; 60 FR 52507, Oct. 6, 1995]

Subpart D—Records and Reports

§ 310.303 Continuation of long-term studies, records, and reports on certain drugs for which new drug applications have been approved.

(a) A new drug may not be approved for marketing unless it has been shown to be safe and effective for its intended use(s). After approval, the applicant is required to establish and maintain records and make reports related to clinical experience or other data or information necessary to make or facilitate a determination of whether there are or may be grounds under section 505(e) of the act for suspending or withdrawing approval of the application. Some drugs, because of the nature of the condition for which they are intended, must be used for long periods of time—even a lifetime. To acquire necessary data for determining the safety and effectiveness of long-term use of such drugs, extensive animal and clinical tests are required as a condition of approval. Nonetheless, the therapeutic or prophylactic usefulness of such drugs may make it inadvisable in the public interest to delay the avail-

ability of the drugs for widespread clinical use pending completion of such long-term studies. In such cases, the Food and Drug Administration may approve the new drug application on condition that the necessary long-term studies will be conducted and the results recorded and reported in an organized fashion. The procedures required by paragraph (b) of this section will be followed in order to list such a drug in § 310.304.

(b) A proposal to require additional or continued studies with a drug for which a new drug application has been approved may be made by the Commissioner on his own initiative or on the petition of any interested person, pursuant to part 10 of this chapter. Prior to issuance of such a proposal, the applicant will be provided an opportunity for a conference with representatives of the Food and Drug Administration. When appropriate, investigators or other individuals may be invited to participate in the conference. All requirements for special studies, records, and reports will be published in § 310.304.

[39 FR 11680, Mar. 29, 1974, as amended at 41 FR 4714, Jan. 25, 1976; 42 FR 15674, Mar. 22, 1977]

§ 310.305 Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.

(a) *Scope.* FDA is requiring manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved new drug or abbreviated new drug application to establish and maintain records and make reports to FDA of all serious, unexpected adverse drug experiences associated with the use of their drug products. Any person subject to the reporting requirements of paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(b) *Definitions.* The following definitions of terms apply to this section:—

Adverse drug experience. Any adverse event associated with the use of a drug in humans, whether or not considered

drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience. Any adverse drug experience that places the patient, in the view of the initial reporter, at *immediate* risk of death from the adverse drug experience as it occurred, i.e., it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

Serious adverse drug experience. Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse drug experience. Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of

greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(c) **Reporting requirements.** Each person identified in paragraph (c)(1)(i) of this section shall report to FDA adverse drug experience information as described in this section and shall submit one copy of each report to the Division of Pharmacovigilance and Epidemiology (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(1) **Postmarketing 15-day "Alert reports".** (i) Any person whose name appears on the label of a marketed prescription drug product as its manufacturer, packer, or distributor shall report to FDA each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the person whose name appears on the label. Each report shall be accompanied by a copy of the current labeling for the drug product.

(ii) A person identified in paragraph (c)(1)(i) of this section is not required to submit a 15-day "Alert report" for an adverse drug experience obtained from a postmarketing study (whether or not conducted under an investigational new drug application) unless the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience.

(2) **Postmarketing 15-day "Alert reports"—followup.** Each person identified in paragraph (c)(1)(i) of this section shall promptly investigate all serious, unexpected adverse drug experiences that are the subject of these postmarketing 15-day Alert reports and shall submit followup reports within 15

calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information. Postmarketing 15-day Alert reports and followups to them shall be submitted under separate cover.

(3) *Submission of reports.* To avoid unnecessary duplication in the submission of, and followup to, reports required in this section, a packer's or distributor's obligations may be met by submission of all reports of serious adverse drug experiences to the manufacturer of the drug product. If a packer or distributor elects to submit these adverse drug experience reports to the manufacturer rather than to FDA, it shall submit each report to the manufacturer within 5 calendar days of its receipt by the packer or distributor, and the manufacturer shall then comply with the requirements of this section even if its name does not appear on the label of the drug product. Under this circumstance, the packer or distributor shall maintain a record of this action which shall include:

- (i) A copy of each adverse drug experience report;
- (ii) The date the report was received by the packer or distributor;
- (iii) The date the report was submitted to the manufacturer; and
- (iv) The name and address of the manufacturer.

(4) Each report submitted to FDA under this section shall bear prominent identification as to its contents, i.e., "15-day Alert report," or "15-day Alert report-followup."

(5) A person identified in paragraph (c)(1)(i) of this section is not required to resubmit to FDA adverse drug experience reports forwarded to that person by FDA; however, the person must submit all *followup* information on such reports to FDA.

(d) *Reporting form.* (1) Except as provided in paragraph (d)(3) of this section, each person identified in paragraph (c)(1)(i) of this section shall submit each report of a serious and unexpected adverse drug experience on an FDA Form 3500A (foreign events may be submitted either on an FDA Form

3500A or, if preferred, on a CIOMS I form).

(2) Each completed FDA Form 3500A should pertain only to an individual patient.

(3) Instead of using Form FDA Form 3500A, a manufacturer, packer, or distributor may use a computer-generated FDA Form 3500A or other alternative format (e.g., a computer-generated tape or tabular listing) provided that:

(i) The content of the alternative format is equivalent in all elements of information to those specified in FDA Form 3500A, and

(ii) The format is agreed to in advance by MedWatch: The FDA Medical Products Reporting Program.

(4) Ten copies or fewer of FDA Form 3500A and/or a copy of the instructions for completing the form may be obtained from the Division of Pharmacovigilance and Epidemiology (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. More than 10 copies of the form may be obtained by writing to the Consolidated Forms and Publications Distribution Center, Washington Commerce Center, 3222 Hubbard Rd., Landover, MD 20785.

(e) *Patient privacy.* Manufacturers, packers, and distributors should not include in reports under this section the names and addresses of individual patients; instead, the manufacturer, packer, and distributor should assign a unique code number to each report, preferably not more than eight characters in length. The manufacturer, packer, and distributor should include the name of the reporter from whom the information was received. Names of patients, individual reporters, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

(f) *Recordkeeping.* (1) Each manufacturer, packer, and distributor shall maintain for a period of 10 years records of all adverse drug experiences required under this section to be reported, including raw data and any correspondence relating to the adverse

drug experiences, and the records required to be maintained under paragraph (c)(4) of this section.

(2) Manufacturers and packers may retain the records required in paragraph (f)(1) of this section as part of its complaint files maintained under §211.198 of this chapter.

(3) Manufacturers, packers, and distributors shall permit any authorized FDA employee, at all reasonable times, to have access to and copy and verify the records established and maintained under this section.

(g) *Disclaimer.* A report or information submitted by a manufacturer, packer, or distributor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the manufacturer, packer, or distributor, or by FDA, that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. The manufacturer, packer, or distributor need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect.

[51 FR 24479, July 3, 1986, as amended at 52 FR 37936, Oct. 13, 1987; 55 FR 11578, Mar. 29, 1990; 57 FR 17980, Apr. 28, 1992; 62 FR 34167, June 25, 1997; 62 FR 52249, Oct. 7, 1997; 67 FR 9585, Mar. 4, 2002]

Subpart E—Requirements for Specific New Drugs or Devices

§310.501 Patient package inserts for oral contraceptives.

(a) *Requirement for a patient package insert.* The safe and effective use of oral contraceptive drug products requires that patients be fully informed of the benefits and the risks involved in their use. An oral contraceptive drug product that does not comply with the requirements of this section is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act. Each dispenser of an oral contraceptive drug product shall provide a patient package insert to each patient (or to an agent of the patient) to whom the product is dispensed, except that the dispenser may provide the insert to the parent or legal guardian of a legally in-

competent patient (or to the agent of either). The patient package insert is required to be placed in or accompany each package dispensed to the patient.

(b) *Distribution requirements.* (1) For oral contraceptive drug products, the manufacturer and distributor shall provide a patient package insert in or with each package of the drug product that the manufacturer or distributor intends to be dispensed to a patient.

(2) Patient package inserts for oral contraceptives dispensed in acute-care hospitals or long-term care facilities will be considered to have been provided in accordance with this section if provided to the patient before administration of the first oral contraceptive and every 30 days thereafter, as long as the therapy continues.

(c) *Contents of patient package insert.* A patient package insert for an oral contraceptive drug product is required to contain the following:

(1) The name of the drug.

(2) A summary including a statement concerning the effectiveness of oral contraceptives in preventing pregnancy, the contraindications to the drug's use, and a statement of the risks and benefits associated with the drug's use.

(3) A statement comparing the effectiveness of oral contraceptives to other methods of contraception.

(4) A boxed warning concerning the increased risks associated with cigarette smoking and oral contraceptive use.

(5) A discussion of the contraindications to use, including information that the patient should provide to the prescriber before taking the drug.

(6) A statement of medical conditions that are not contraindications to use but deserve special consideration in connection with oral contraceptive use and about which the patient should inform the prescriber.

(7) A warning regarding the most serious side effects of oral contraceptives.

(8) A statement of other serious adverse reactions and potential safety hazards that may result from the use of oral contraceptives.

(9) A statement concerning common, but less serious side effects which may help the patient evaluate the benefits